REMARKS

Claims 69-80, 124-127, 129, 130, 136-173, 186 and 190 are pending. Claims 1-68, 81-123, 128, 131-135, 174-185 and 187-189 are cancelled. Claims 69, 70, 72-80, 124-127, 129, 130, 136-159, 164, 166-173 and 186 have been amended. Claims 70, 72-80, 129, 130, 136-159, 164, 166-173 and 186 have been amended for clarity and to fix typographical errors. Claims 69 and 124-127 have been amended to remove language reciting "preventing or delaying progression", and this subject matter is now presented in new claim 190. Support for the new claim and the amendments can be found, for example, at page 19, lines 37-38, page 29, lines 13-15, and throughout the application as originally filed. No new matter has been added.

Rejection of Claims 69-80, 124-127, 129, 130, 136-173 and 186-189 Under 35 U.S.C. §112, first paragraph

Claims 69-80, 124-127, 129, 130, 136-173 and 186-189 are rejected under 35 U.S.C. §112, first paragraph, for "scope of enablement for the reasons of record with regards to the prevention of prostate cancer".

Applicant respectfully disagrees with this assertion. However, in the interest of expediting prosecution of the application, the claims have been amended and are now directed to methods of treating prostate cancer. Support for the amendments can be found at, e.g., page 19, lines 37-38, and page 29, lines 13-15. New claim 190 has been added that indicates that prevention of the progression of prostate cancer is encompassed by the methods of treatment. The Examiner states that "to obviate this rejection, Applicants should review the interview summary mailed 05/26/04, which discussed the present rejection." As the amendments to the claims and the presentation of new claim 190 are consistent with the interview summary mailed May 26, 2004, this rejection is obviated.

Further, Applicant has provided the Examiner with evidence that treatment of patients having prostate cancer with the claimed antibodies prevents the progression of prostate cancer. See Exhibit A (submitted herewith) that reports that in patients with metastatic androgen-independent prostate cancer, treatment with the antibody J591 (referred to as MLN591 in

Exhibit A) improved extensive cutaneous metastatic lesions and prevented the progression of prostate cancer. Thus, the amendments to the claims obviate this rejection, and new claim 190 is fully enabled.

Claims 69-80, 124-127, 129, 130, 136-173 and 186-189 are further rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner asserts that "the written description is not commensurate in scope with the claims drawn to an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody."

Applicant respectfully traverses this rejection. The application clearly provides sufficient description of antibodies that compete for binding to PSMA with the recited antibodies such that a skilled artisan would recognize that Applicant was in possession of the claimed invention at the time of filing.

The written description requirement is met if the specification shows that an applicant was in possession of the claimed invention at the time of filing. "When the original specification accomplishes [this], regardless of *how* it accomplishes it, the essential goal of the description requirement is realized." *In re Smith*, 481 F.2d 910, 914 (CCPA 1973). It is well accepted that "in order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *ad haec verba* support for the claimed subject matter at issue". *Purdue Pharma v. Faulding, Inc.*, 56 USPQ 2d 1481 (Fed. Cir. 2000); and MPEP § 2163.02. As provided, for example, in *In re Wright*, 866 F.2d 422 (Fed. Cir. 1989), "the fact...that the exact words here in question...are not in the specification is not important" (emphasis added). In *Wright*, the claims at issue involved methods for forming images and included a step of depositing a layer of microcapsules in the form of a free flowing powder. The claims recited that the layer of microcapsules was "not permanently fixed". The Examiner rejected claims with this language,

asserting a lack of written description. On appeal, the Federal Circuit held that the original specification unequivocally taught the absence of permanently fixed microcapsules, as demonstrated by a description of the removal of microcapsules from the surface and a warning that the capsules should not be disturbed prior to the formation of the image, and that the written description rejection "was clearly erroneous".

Here, the claimed invention involves a method that uses an antibody having a specific feature: it competes for binding PSMA with a specific, disclosed antibody, namely E99, J591, J415 or J533. The support for this language in the specification of the above-identified application is even clearer than the situation presented in *Wright*. As provided in the Declaration of Abbie Celniker under 37 CFR § 1.132 (hereafter "the Declaration", filed herewith), one of ordinary skill in the art at the time the application was filed would have found that the specification discloses and that Applicant was in possession of antibodies that compete for binding with one of the specifically disclosed antibodies. Specifically, the Declaration points to page 27 lines 26-35 of the specification of the above-identified application as filed. This passage discusses a particular embodiment wherein antibodies are used to direct two components to a desired site, and provides as follows:

> ***a first biological agent*** is conjugated with a prodrug which is activated only when in close proximity with a prodrug activator. The prodrug activator is conjugated with ***a second biological agent according to the invention, preferably*** one which binds to a non-competing site on the prostate specific membrane antigen molecule. Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays. (***emphasis added***).

From the passage recited above, it would be clear to one of ordinary skill in the art at the time the application was filed that the cited text, in combination with the rest of the specification, discloses two types of antibodies --those that compete for binding with an antibody "according to the invention" and those that do not compete for binding with an antibody "according to the invention", the later being preferred in the particular embodiment being described. But whether preferred or not, it is clear from the text that Applicant was in possession of the idea of an antibody which competes for binding with an antibody according to the invention. The text also

provides, see, e.g., the last sentence of the quoted passage, what constitutes a competing site and a non-competing site by stating that "whether two biological agents bind to competing or non-competing sites can be determined by conventional competition binding assays." Therefore, the application necessarily discloses the concept of an antibody that competes for binding with an antibody according to the invention. Thus, a person of ordinary skill in the art at the time the application was filed would have believed that the concept of having an antibody that competes for binding with "an antibody according to the invention" is necessarily part of the disclosure of the present application and that Applicant was in possession of this element of the invention at the time of filing.

As provided in the Declaration, it is also clear that, upon reviewing the specification of the above-referenced application, one of ordinary skill at the time the application was filed, would have believed that monoclonal antibodies E99, J415, J533 and J591 are "antibodies according to the invention." These four antibodies are disclosed throughout the application as being antibodies of the invention. In fact, the very next sentence, at page 28, lines 1-6, after the passage recited above states as follows:

> For example, monoclonal antibodies J591, J533, and E99 bind to competing binding sites on the prostate specific membrane antigen molecule. Monoclonal antibody J415, on the other hand, binds to a binding site which is non-competing with the site to which J591, J533, and E99 bind.

Thus, the application necessarily discloses that monoclonal antibodies E99, J415, J533 and J591 are antibodies according to the invention. Given that J415, J591, J533 and E99 are antibodies of the invention, and that the specification clearly supports the concept of antibodies that compete for binding with an antibody of the invention, a skilled artisan would recognize that the application discloses and that Applicant was in possession of antibodies that compete for binding with J415, J591, J533 or E99. The text of the specification describes and shows possession of the claimed subject matter.

Claims 82, 84 and 110-120 are also rejected "as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention." These claims have been cancelled, thereby obviating this rejection.

For the reasons discussed above, Applicant respectfully requests that the Examiner withdraw this rejection and allow all the currently pending claims.

Enclosed is a Declaration under 37 CFR § 1.132. No fee is believed to be due. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 13 August 2004

Rolando Medina, Ph.D., J.D.
Reg. No. 54,756

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

EXHIBIT A

Phase 1 trial of MLN2704 in patients with metastatic androgen-independent prostate cancer

Background: MLN2704 is an antibody targeted chemotherapeutic designed to deliver the maytansinoid anti-microtubule agent DM1 to prostate cancer cells through the targeting of MLN591, a deimmunized monoclonal antibody to prostate-specific membrane antigen (PSMA). Robust preclinical models have indicated significant activity in xenograft models. We report the results of the first Phase 1 trial of MLN2704 in patients with metastatic androgen-independent prostate cancer (AIPCa).

Methods: The study was designed to determine the MTD, DLT, PK and immunogenicity of a single ascending dose of MLN2704. Based on emerging clinical safety and PK, repeat dosing at 4-week intervals was subsequently permitted. Eligibility criteria included men with progressive metastatic AIPCa, acceptable baseline performance status, hepatic and hematologic function. DLT was defined as platelets<10,000, requirement for platelet transfusion or G-CSF, febrile neutropenia, ANC<500 of 7 days, severe anemia, or any Grade≥3 nonhematologic toxicity related to study drug.

Results: 23 patients have received MLN2704 at doses ranging from 18 to 343 mg/m^2 in this ongoing clinical trial. 17 patients have received three doses. PK of antibody related analytes (J591-DM1, Total J591 and free J591) was typical of monoclonal antibodies. Plasma levels of DM1-SH were detectable. No anti-antibodies against MLN2704, MLN591 or DM1 were detected. MLN2704 has been well-tolerated in the majority of patients. Only one DLT, an uncomplicated febrile neutropenia, has been reported at the highest dose level (343 mg/m^2). This patient also demonstrated a sustained >50% PSA decline and remains on study at a reduced dose. One patient treated at the 264 mg/m^2 dose level has experienced a PR by RECIST criteria, improvement in extensive cutaneous metastatic lesions as well as durable 70% decrease in PSA. This patient has received seven doses and remains on study at 24 weeks without evidence of disease progression or significant toxicity. Additional patients have experienced pain relief, stabilization of PSA, and improved performance status.

Conclusions: Anti tumor activity has been observed at well-tolerated doses of MLN2704. MTD is $\geq$ 343 mg/m^2.